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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/001,267	10/31/2001	Lakshmi Rambhatla	093/004P	1874

22869 7590 11/23/2005

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/001,267	RAMBHATLA ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-15,19-24,26-32 and 34-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-15,19-24,26-32 and 34-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/1/05 has been entered.

Applicants' After-Final amendment, filed 7/18/05, has been entered. Claims 13, 2728-30 have been amended; claims 1-12, 16-18, 25, 33, 39-40 are cancelled; claims 13-15, 19-24, 26-32, 34-38 are pending and under current examination.

The Examiner addresses Applicants' arguments, filed with the After-Final Amendment, 7/18/05.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The prior rejection of claims 13-15, 19-24, 26-32, 34-38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6, 7, 9-13 17-19 of copending Application No. 10/087,142 is maintained for reasons of record advanced in the Office action mailed 12/15/04. Applicants acknowledge the rejection and state that upon indication of patentable subject matter, Applicants undertake to file a terminal disclaimer or to take other appropriate action to obviate double patenting. (See Response, filed 6/9/04, p. 7).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The prior rejection of claims 13-40 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,458,589 B1 [published October 1, 2002] is withdrawn. The Examiner reiterates that the arguments presented in the Response is found to be persuasive, namely that there is nothing that ties the claims of this issued patent to those of the instant invention, because butyrate is not in the claimed product of the '589 patent.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-15, 19-24, 26-32, 34-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for

producing hepatocytes from primate pluripotent stem (pPS) cells, comprising a) obtaining a culture of pPS cells; b) initiating differentiation of the pPS cells of the pPS cells simultaneously or subsequently, c) culturing the cells of step (b) in a medium containing 5 mM sodium butyrate until at least 60% of the cultured cells have at least three of the characteristics: antibody detectable expression of AAT, antibody-detectable expression of albumin, absence of antibody-detectable expression of α-fetoprotein, RT-PCR detectable expression of ASGR, evidence of glycogen storage, evidence of cytochrome p450 activity, evidence of glucose-6-phosphate activity, or the morphological activity of hepatocytes, does not reasonably provide enablement for the breadth of the claims which recite culturing the cells in a medium containing any concentration of butyrate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection is maintained for reasons of record advanced in the Office action mailed 12/15/04.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants argue that it is unnecessary for the claims to indicate the concentration of butyrate needed to effect differentiation into hepatocytes lineage cells, the specification exemplifies butyrate concentrations that are effective, and should the reader decide to deviate from the exemplified concentration, this can be done without undue experimentation – the protocol is just repeated at an altered butyrate concentration, and the cell culture is monitored for the presence of hepatocytes lineage cells having the characteristics required by the claim.

Applicants further argue that the skilled reader can use the same empirical approach in order to determine what other histone deacteylase inhibitors are effective in making hepatocytes lineage cells from pPS cells. Applicants have now amended the claims to recite butyrate to overcome the prior rejection. See Applicants' Response, page 7.

These arguments have been considered, but are not persuasive. Applicants have provided one working example, using 5 mM sodium butyrate that arrives at the instantly claimed invention. The claims require that the conditions be capable of producing about 60% cells that express hepatocytes characteristics. In specific embodiments, the claims require that at least 80% of the cells have at least 7 of these characteristics (see claim 15, for example). The breadth of the claims encompasses using any concentration of butyrate, and any type of butyrate. The instant specification teaches that butyrate has a differentiating and modulating effect on cell types other than ES cells (such as acute myeloid leukemia cells, an in the induction of erythroblastic differentiation). See p. 7, lines 20-25 and p. 8, lines 3-5. The specification teaches that sodium butyrate is the differentiation agent used in the instant specification, but contemplates a number of n-butryate homologues and derivatives, which are encompassed by the claims. See p. 17, Suitable Differentiation Agents, particularly, lines 35-39. Table 4 summarizes the culture of human ES cells in 5 mM sodium butyrate and show that these culture condition result in over 60% of the cells having the requisite characteristics of hepatocytes. Table 7 summarizes the induction of ES cells to the hepatocytes phenotype using various hepatocytes differentiation agents (which include various forms/structural analogs of butyrate, such as propionic acid, isovaleric acid, and isobutryric acid). However, these results fail to enable the claimed invention, because they fail to teach that at least 60% of the cells, under these conditions, would be hepatocytes. Indeed, Table 7 shows the unpredictability in using various hepatocytes differentiation agents. For example, isobutryic acid provides a

phenotype that is deemed to have a mild inductive effect that may allow for the growth and survival of other cell types. The specification only provides guidance with regard to a specific concentration of a specific histone deacteylase inhibitor, 5 mM sodium butyrate.

Accordingly, in view of the state of the art of directed differentiation of ES cells to hepatocytes (cited in the prior Office action), the lack of guidance or direction by the specification with regard to the production of ~60% hepatocytes using any butyrate in any concentration, the lack of working examples provided by the specification with regard to the use of other analogs of butyrate to successfully arrive at the claimed invention, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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